REMARKS

Claims 1-6 are pending. For the Examiner's convenience, a listing of the claims is attached hereto.

The sole remaining issue is a new rejection which, according to the Examiner, was necessitated by Applicants' previous response. For reasons set forth below, the claims are not obvious and should be deemed allowable.

1. The Claims Are Not Obvious

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being obvious over United States Patent No. 4,675,286 by Calenoff ("Calenoff") in view of Chaiken et al., 1986, Proc. R. Soc. Lond. A408:165-174 ("Chaiken"). The Examiner states:

> The Calenoff patent discloses a method of separating fetal cells from maternal cells by using a separation antibody which preferentially binds to fetal cell antigens (abstract). The reference further discloses that the antibodies can be coupled to solid surfaces such as plastic or glass containers, etc. (col. 5, lines 13-30). Example #3 of the patent discloses that the method includes slowly stirring the reaction mixture for 1 hour. The reference is silent as to the use of the device defined in the claims for creating chaotic flow. The Chaiken et al. article discloses that it is advantageous for achieving efficient stirring to create chaotic advection (page 166, beginning of the 3rd paragraph). The article further describes the same device used and claimed by applicant for creating chaotic flow (page 169). Since the apparatus disclosed in figure 2 of Chaiken et al. is used to created *[sic]* chaotic flow for optimized stirring, it would have been obvious to one skilled in the art to use the device in the method disclosed in Calenoff for stirring the reaction mixture.

Applicants assert that the claims are not obvious over Calenoff in view of Chaiken, for the following reasons.

First, the Examiner combines Calenoff with Chaiken based on the teaching of Example #3 that a reaction mixture is slowly stirred for one hour. Applicants

respectfully point out that the Examiner has misinterpreted Example #3. The reaction mixture stirred in Example #3 is a preparation step that bears no relationship whatsoever to maternal or fetal cells. The mixture contains magnetic microspheres and *Staphylococcus* protein A, is a step in the preparation of magnetic microspheres coupled to anti-trophoblast antibodies, and contains no fetal (target) cells. Furthermore, the stirring referred to occurs during only part of the preparation, while the glutaraldehyde is added, and not during the subsequent hour. Examples 5 and 6 of Calenoff refer only generally to mixing (that is to say, combining) cells and antibodies conjugated to fluorescent label or magnetic microspheres and these agents are not adhered to a solid surface of a vessel. While Calenoff envisages adherence of antibodies to solid surfaces,[1] there is no disclosure as to how the cell sample could be mixed or circulated over such surfaces. The only mixing expressly referred to involves the mixing of suspended particles.

Second, the disclosure of Calenoff which is incremental to its prior art involves using placental tissue as a source of fetal cells. Calenoff admits that the use of antibodies specific for cell surface markers as a means for separating cells is old (Calenoff, column 2 lines 3-37), as are the affixing of such antibodies to solid supports (Calenoff, column 2 lines 38-49). Thus, the distinguishing feature of Calenoff's technology, the collection of fetal cells originating from the placenta "obtained from areas between the walls of the uterine cavity and the external surface of the amniotic sac,"[2] is completely different from the source of cells used according to the invention, namely a maternal blood sample. Fetal cells occur in the context of different maternal

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1 Calenoff, column 5 lines 54-56.
2 Calenoff, column 1 lines 6-11.

cells in the samples evaluated by Calenoff or the invention (a sample taken by a swab or probe inserted through the mucus plug of the uterine canal according to Calenoff,[3] and a blood sample according to the invention). One would expect that the ratio of fetal to maternal cells would be lower in the maternal blood sample utilized according to the invention. The issues involved in the separation of fetal and maternal cells in the samples tested by Calenoff or the present invention would therefore not be expected to be the same.

Third, and very importantly, the nature of the objects being mixed is substantially different in Calenoff, Chaiken, and the claimed invention. Example #3 aside, Calenoff discloses mixing (in the sense of combining) fetal cells with antibodies bound to fluorescent label (Example #5) or magnetic beads (Example #6). The mixing of cells and antibody molecules generally alluded to in Calenoff is clearly different from the mixing studied in Chaiken, which specifically relates to the dispersal of dye in solution. Chaiken considers "real-world" physical manifestations of chaotic advection to include "the observed patterns formed by cream floating on the surface of coffee or films of oil flowing down a street on a rainy day."[4] It would not be obvious to extend this characterization of chaotic advection systems to mixtures of living cells.

But the types of mixing disclosed in Calenoff or Chaiken both differ from the specific kind of mixing (chaotic advection) used in this invention and recited in the claims. According to the present invention, the already mixed combination of maternal and fetal cells in a maternal blood sample are circulated, in a vessel, by chaotic advection so that there is an enhanced likelihood that the few fetal cells present will encounter the

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[3] Calenoff, column 3 lines 50-64.

[4] Chaiken, p. 173, end of next-to-last paragraph.

"collector surface" of a vessel onto which a ligand specific for fetal cells is bound. Despite being very different in their teachings, both Calenoff and Chaiken relate to the way suspended entities are mixed. Neither address the issue of enhancing the likelihood that a free floating cell would come in contact with a collector surface of a vessel.

In contrast, the present invention uses chaotic advection to improve the probability that a fetal cell will encounter the collector surface. This approach constitutes a nonobvious use of chaotic advection: the same phenomena that disperse initially concentrated particles to form a uniform mixture can be used to collect the particles when the surface of a container is rendered adhesive - that is, the opposite of dispersion (namely, concentration) can be achieved. In this way, the invention provides an effective and rational solution to the problem presented by the low percentage of fetal cells in a maternal blood sample. Neither Calenoff nor Chaiken discloses or suggests such a solution.

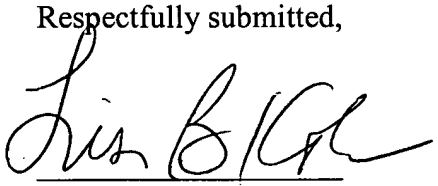
To summarize, the present invention relates to a method for efficiently circulating a maternal blood sample, containing an extremely small number of fetal cells, by a specific form of mixing- chaotic advection- to enhance the likelihood that the fetal cells will encounter a selectively adherent collector surface. Neither of the cited references, nor their combination, render this method obvious. Calenoff's unique feature involves the source of fetal cells. Chaiken discloses chaotic advection, but only as manifested by the dispersal of dye in liquid. Because Calenoff relates to cells and antibodies, and Chaiken relates to dispersal of dye particles in liquid, they should not be combined to form an obviousness rejection. However, *if they are combined*, because Calenoff and the invention utilize different sources for fetal cells (exfoliated trophoblasts

in a cytologic sample in Calenoff and maternal blood according to the invention), because Chaiken relates to mixing in a system having different physical characteristics from Calenoff or the present invention (dye (Chaiken) versus cells and antibodies (Calenoff) versus cells that encounter an adherent surface (the invention)), because the mixing expressly addressed in Calenoff and Chaiken relates to suspended entities, and because neither reference discloses using chaotic advection to enhance the likelihood that a suspended entity will encounter a fixed surface and thereby enrich the population of fetal cells collected, they cannot render the claimed invention obvious.

Conclusion

In view of the foregoing remarks, Applicants respectfully request that all pending claims be deemed allowable.

Respectfully submitted,



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CLAIM LISTING

1. (previously presented) A method for collecting fetal cells from a maternal blood sample, comprising the steps of:

disposing a liquid comprising the maternal blood sample in a vessel having (i) an interior comprising a movable outer portion and a movable inner portion and (ii) a collector surface bearing a ligand specific for the fetal cells; and

effecting a chaotic flow in the liquid by alternately moving the outer portion and inner portion of the vessel relative to each other so as to repeatedly switch from one laminar flow to another for a duration of time effective for binding fetal cells to the ligand on the collector surface.

2. (previously presented) The method according to claim 1, wherein the vessel comprises a rotatable outer portion and a rotatable inner portion whose axes of rotation are distinct rather than coincident.

3. (original) The method according to claim 2, wherein the step of effecting the chaotic flow comprises rotating each of the outer and inner portions of the vessel in an alternating fashion.

4. (previously presented)The method according to claim 1, wherein the collector surface is disposed at the outer portion of the vessel.

5. (previously presented) The method according to claim 1, wherein the collector surface is disposed at the inner portion of the vessel.

6. (previously presented) The method according to claim 1, wherein the collector surface is disposed on at least one surface immersed in the liquid.

7 – 18. (cancelled)